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Synthesis of 5-(diethoxyphosphoryl)-substituted hydrogenated pyrimidine-2-thiones

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Abstract: The reaction of sodium enolate of diethyl (2-oxoprop-1-yl)phosphonate with *N*-(1-tosylprop-1-yl)thiourea results in a stereoselective formation of diethyl (4R*,5R*,6R*)-6-ethyl-4-hydroxy-4-methyl-2-thioxohexahydropyrimidine-5-phosphonate which is transformed into diethyl 4-ethyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-phosphonate and diethyl (4R*,5S*,6R*)-4-ethyl-6-methyl-2-thioxohexahydropyrimidine-5-phosphonate by acid-catalysed dehydration and stereoselective reduction with $NaBH_4$ - CF_3COOH, respectively.

Keywords: b-oxophosphonates, a-tosyl-substituted thioureas, thioureidoalkylation, 5-(diethoxyphosphoryl)-substituted hydrogenated pyrimidine-2-thiones, reduction, acyliminium cations

Introduction

Hydrogenated pyrimidin-2-ones/thiones bearing functional group at the fifth position (e.g., **1** and **2**) are of interest because of their biological activity. For instance, esters of 4-aryl-2-oxo(or 2-thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acids (**1** R' = aryl, FG = COOR"), Biginelli compounds, are inhibitors of kinesin Eg5 [1], selective antagonists of a1à-adrenoceptors [2], possess high antihypertensive activity [3, 4], etc.

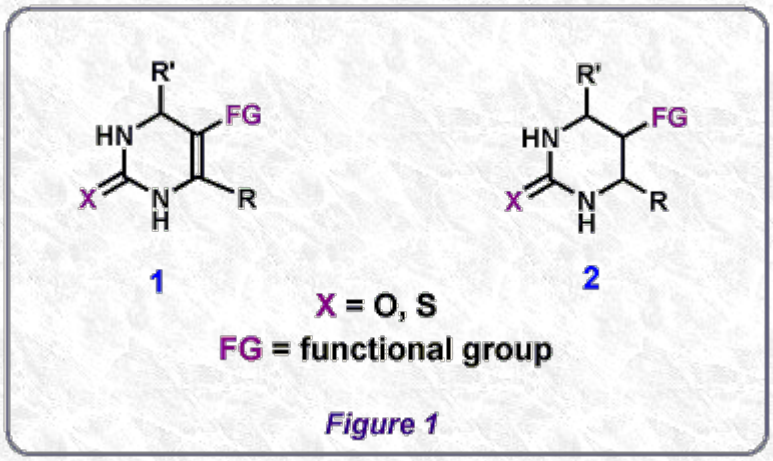
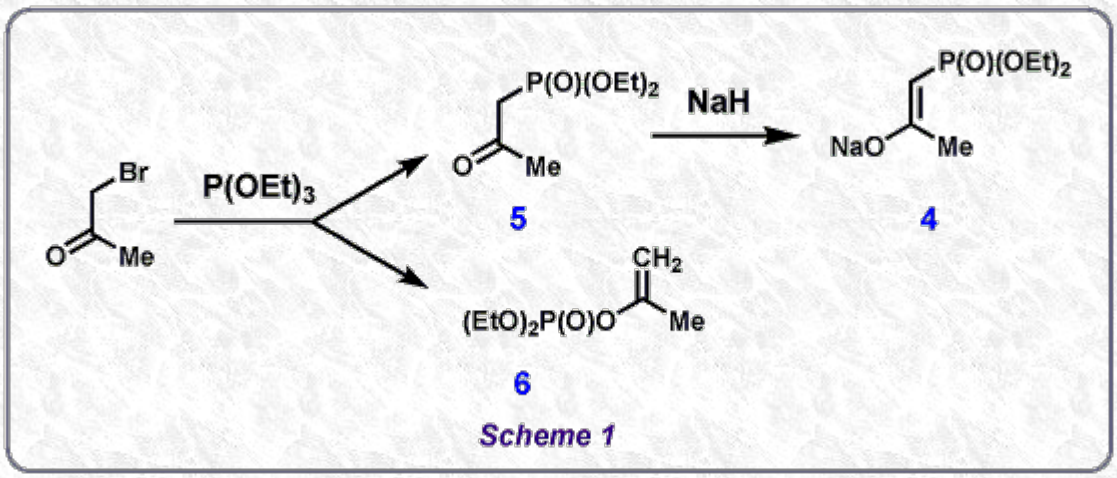


Figure 1

Pyrimidines **1** bearing carboxamide (**1** FG = CONR"R"') [5], carboxyl (**1** FG = COOH) [6], cyano (**1** FG = CN) [7], acyl (**1** FG = COR") [8], nitro (**1** FG = NO_2) [9], sulphonyl groups (**1** FG = SO_2R") [10] and halogen atoms [11] at C(5) are also investigated as compounds with potential biological activity. However, 1,2,3,4-tetrahydro- (**1**) and hexahydropyrimidin-2-ones/thiones (**2**) bearing phosphorus atom at the fifth position remain poorly studied. Only one recent communication [12] describes the synthesis of some esters of 4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-phosphonic acids (**1** R' = aryl, FG = $PO(OEt)_2$) by the reaction of urea with diethyl (2-oxoprop-1-yl)phosphonate and aromatic aldehydes in the presence of ytterbium triflate. Thus, the development of general synthetic methods for preparation of pyrimidines with organophosphorous moieties at C(5) atom, particularly phosphoryl groups, is relevant. We report the synthesis of some diethyl 2-thioxo-1,2,3,4-tetrahydro- and hexahydropyrimidine-5-phosphonates.

Results and Discussion

Diethyl 6-ethyl-4-hydroxy-4-methyl-2-thioxohexahydropyrimidine-5-phosphonate (**3**) served as a key heterocyclic compound. It was obtained by the general method of 5-functionally substituted hydrogenated pyrimidin-2-ones/thiones synthesis which is based on the reaction of enolates of a-functionalized aldehydes or ketones with a-tosyl-substituted ureas/thioureas [13, 14]. We used sodium enolate (**4**) of diethyl (2-oxoprop-1-yl)phosphonate (**5**) as a nucleophile for pyrimidine **3** preparation. Compound **5** was obtained as described in ref. [15, 16] by heating bromacetone with triethylphosphite at 165-170 îÑ without solvent (*Scheme 1*).

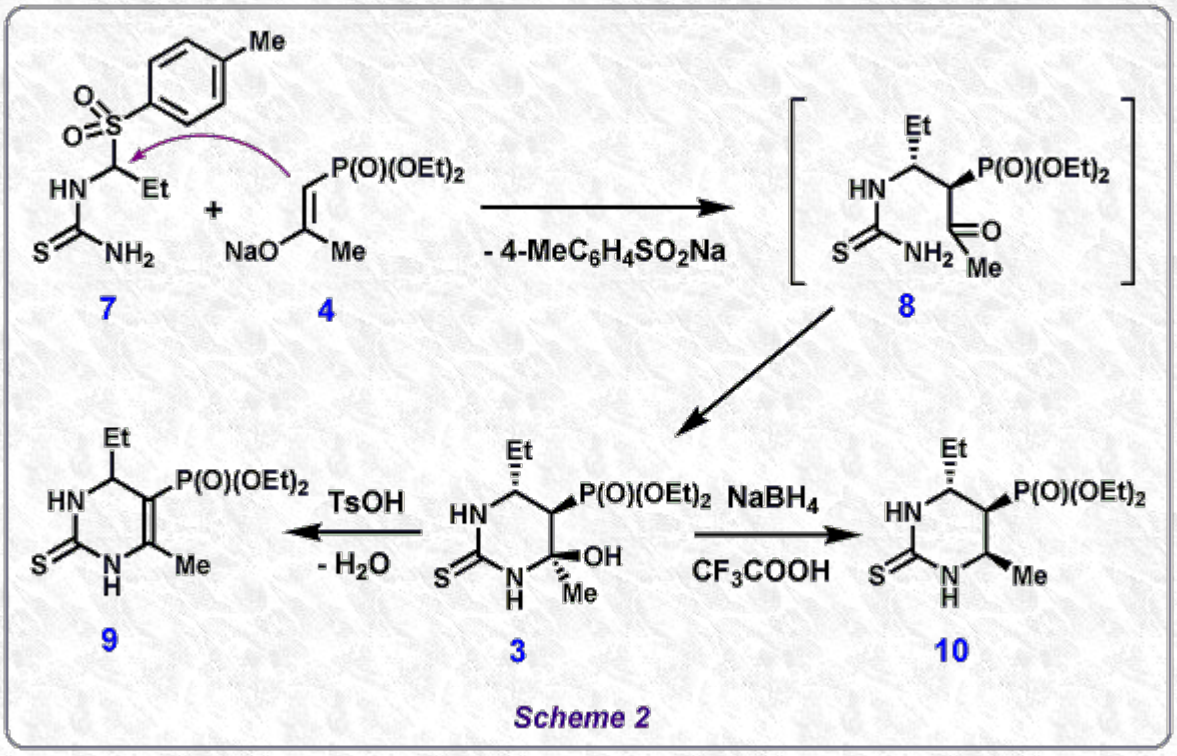


Scheme 1

A considerable amount of ester **6** (up to 20 % according to ^{1}Í NMR data) forms in this reaction along with phosphonate **5**. It appeared rather difficult to separate these substances effectively by simple

distillation *in vacuo*. The presence of **6** in **5** strongly decreased the yield of pyrimidine **3**. Therefore it was necessary to develop a convenient procedure to purify phosphonate **5**. This problem was solved by the treatment of the ether solution of a mixture of **5** and **6** with a known ratio of the components by calculated amount of NaH. The precipitated sodium enolate **4** was filtered, dried and used in further reactions without additional purification.

We have found that enolate **4** reacted with readily available *N*-(1-tosylprop-1-yl)thiourea (**7**) [14] in dry THP for 8 h at r.t. to produce the expected hydroxypyrimidine **3** in 81 % yield (*Scheme 2*).



Scheme 2

It is noteworthy that both stages of compound **3** formation (nucleophilic substitution of tosyl group in **7** and subsequent heterocyclisation of intermediate thiourea **8**) proceeded with high diastereoselectivity. ^{1}Í NMR spectrum of crude **3** showed a single diastereomer. The value of vicinal coupling constants of 6-H with 5-H and N(1)-Í in this diastereomer ($J_{5\text{-H},6\text{-H}}$ = 11.7, $J_{N(1)H,6\text{-H}}$ = 0 Hz) reveals diequatorial orientation of ethyl and diethoxyphosphoryl groups. The orientation of substituents at quaternary Ñ(4) atom was determined from the ^{1}H-^{1}H NOESY spectrum in DMSO-*d*$_6$. Cross-peaks between the hydrogen of OH group and axial hydrogen 6-H as well as between the hydrogens of 4-CH_3 group and axial hydrogen 5-H indicate that the orientation of hydroxyl group is axial. This was confirmed by the presence of distant coupling constant between OH proton and axial 5-H proton ($J_{OH,5\text{-H}}$ = 1.2 Hz). Thus, the obtained compound has (4R*,5R*,6R*)-configuration.

Hydroxypyrimidine **3** easily dehydrates in the presence of *p*-toluenesulphonic acid in reflux ethanol for 1.5 h to give diethyl 1,2,3,4-tetrahydropyrimidine-5-phosphonate **9** in 89 % yield (*Scheme 2*) (Method A). The latter can be also obtained directly from sulphone **7** with 73 % overall yield without isolation of **3**. For this purpose *p*-toluenesulphonic acid is added to the reaction mixture formed by the reaction of **7** with 4 (THP, 20 îÑ, 7 h) followed by heating at reflux for 2 h (Method Â).

Previously we have shown that $NaBH_4$ - CF_3COOH readily reduces 5-unsubstituted 1,2,3,4-tetrahydro- and 4-hydroxy(or 4-alkoxy)hexahydropyrimidin-2-ones/thiones [17]. This reducing agent we used for preparation of diethyl hexahydropyrimidine-5-phospfonate **10** from **3**. The expected hexahydropyrimidine **10** was obtained after adding the excess of CF_3COOH to pyrimidine **3** and $NaBH_4$ (molar ratio 1:8) mixture in THP at 0 îÑ followed by stirring the obtained solution for 7 h at

r.t. (*Scheme 2*). The yield of recrystallized product was 65 %.

It should be noted that reduction of **3** involving chiral Ñ(4) atom proceeded with high diastereoselectivity. Compound **10** formed as a single stereoisomer with (4R*,5S*,6R*)-configuration according to ^{1}Í NMR spectrum of crude product. This follows from analysis of coupling constants between N(1)-H, N(3)-H, 4-H, 5-H and 6-Í protons. In contrast to compound **3** which exists in the conformation of a slightly flat chair, compound **10** in DMSO-d_6 has the conformation of a distorted chair with *pseudo*-axial orientation of 6-CH_3 group and *pseudo*-equatorial orientation of 4-C_2H_5 group. This conclusion is based on the values of the following coupling constants: $J_{4\text{-H},5\text{-H}}$ = 7.0, $J_{5\text{-H},6\text{-H}}$ = 4.3, $J_{\text{N(3)H},4\text{-Í}}$ = 2.3 and $J_{\text{N(1)H},6\text{-Í}}$ = 3.0 Hz.

The stereoselectivity of hydroxypyrimidine **3** reduction can be explained in terms of S$_N$1 mechanism *via* formation of practically planar acyliminium cation. Subsequent hydride ion transfer from the bulky sodium tris(trifluoroacetoxy)borohydride [18], which is formed by the reaction of $NaBH_4$ with excess of CF_3COOH, occurs preferably from the side opposite to diethoxyphosphoryl group.

Conclusion

Thus, we developed the synthetic method for preparation of previously unknown derivatives of 2-thioxo-1,2,3,4-tetrahydro- and 2-thioxohexahydropyrimidine-5-phosphonic acids. This method includes stereoselective formation of diethyl 4-hydroxy-2-thioxohexahydropyrimidine-5-phosphonates and their transformations. The method is general and gives access to different hydrogenated pyrimidine-2-ones/thiones bearing dialkoxyphosphoryl groups at the fifth position, which will be the subject of our further publications.

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